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D-Dimer Trends Predict Recurrent Stroke in Patients with Cancer-Related Hypercoagulability

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Keywords
Cancer-related stroke · Hypercoagulability · D-dimer · Trousseau syndrome

Abstract
Introduction: In patients with cancer-associated hypercoagulability (CAH)-related stroke, D-dimer trends after anticoagulant therapy may offer a biomarker of treatment efficacy. The purpose of this study was to clarify the association between D-dimer trends and recurrent stroke after anticoagulant therapy in patients with CAH-related stroke. ***Methods:*** We performed retrospective cohort study of consecutive patients with CAH-related stroke at two stroke centers from 2011 to 2020. The ratio of posttreatment to pretreatment D-dimer levels (post/pre ratio) was used as an indicator of D-dimer trends after anticoagulant therapy. Fine-Gray models were used to evaluate the association between post/pre ratio and recurrent stroke. ***Results:*** Among 360 acute ischemic stroke patients with active cancer, 73 patients with CAH-related stroke were included in this study. Recurrent stroke occurred in 13 patients (18%) during a median follow-up time of 28 days (interquartile range, 11–65 days). Multivariate analysis revealed that high post/pre ratio was independently associated with recurrent stroke (per 0.1 increase: hazard ratio 2.20, 95% confidence interval 1.61–3.01, $p = 0.012$). ***Conclusion:*** D-dimer levels after anticoagulant therapy were associated with recurrent stroke in CAH-related stroke patients. Patients with neutral trends in high D-dimer levels after anticoagulant therapy were at high risk of recurrent stroke.

Introduction

Cancer patients are at high risk of stroke due to cancer-related mechanisms [1–6]. Of these, cancer-associated hypercoagulability (CAH) is the main cause of ischemic stroke [6–8]. CAH-related stroke is characterized by a high risk of early recurrent stroke as well as high D-dimer levels and multiple vascular territory infarctions (MVTIs) [8–13]. Although there are no widely accepted diagnostic criteria, CAH-related stroke is typically diagnosed when the following conditions are met: (1) a high pretreatment D-dimer value; (2) MVTIs; or (3) no other specific cause of stroke can be identified [6, 14].

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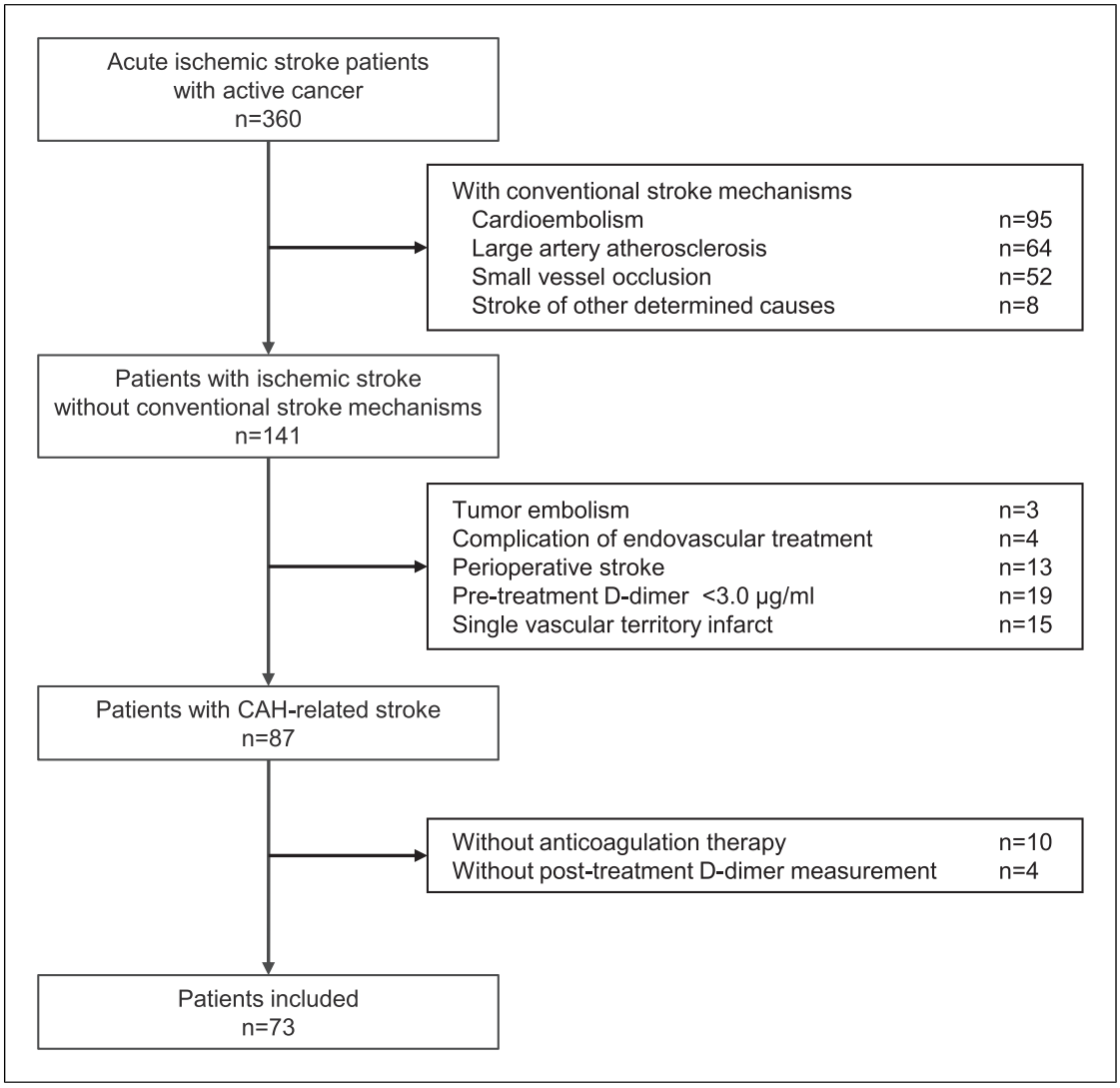

Fig. 1. Flow diagram of inclusion and exclusion criteria.

Though no widely accepted treatment options for CAH-related stroke exist, anticoagulant therapy can correct hypercoagulability and reduce D-dimer levels in cancer patients [15–18]. D-dimer trends have been considered as a possible biomarker of treatment efficacy, and D-dimer levels after treatment have been demonstrated to be associated with survival rates [18–20]. However, the association between D-dimer trends and recurrent stroke has not been fully investigated. The purpose of this study was to clarify the association between D-dimer trends and recurrent stroke after anticoagulant therapy in patients with CAH-related stroke.

Methods

Design

This was a retrospective cohort study of patients diagnosed with CAH-related stroke in a university hospital (Kyoto Prefectural University of Medicine, Kyoto, Japan) and a tertiary stroke center (Kyoto Second Red Cross Hospital, Kyoto, Japan).

Study Patients

Among the 360 acute ischemic stroke patients with active cancer admitted to the two participating institutions within 7 days after onset between January 2011 and December 2020, we enrolled patients diagnosed with CAH-related stroke. Acute ischemic stroke was defined as any new neurological symptom with acute ischemic lesions confirmed by diffusion-weighted imaging (DWI).

Table 1. Baseline characteristics of CAH-related stroke patients

	Total (*n* = 73)
Age, years, median (IQR)	70 (66–77)
Women, *n* (%)	38 (52)
Hypertension, *n* (%)	24 (33)
Dyslipidemia, *n* (%)	16 (22)
Diabetes mellitus, *n* (%)	12 (16)
Current smoking, *n* (%)	12 (16)
Deep venous thrombosis, *n* (%)	26 (36)
Pancreas cancer, *n* (%)	22 (30)
Lung cancer, *n* (%)	14 (19)
Gastric cancer, *n* (%)	9 (12)
Ovarian cancer, *n* (%)	7 (10)
Biliary tract cancer, *n* (%)	6 (8)
Adenocarcinoma, *n* (%)	52 (71)
Squamous cell carcinoma, *n* (%)	4 (5)
Systemic metastases, *n* (%)	65 (89)
Recent chemotherapy, *n* (%)	27 (37)
DWI three territory sign, *n* (%)	57 (78)
Pretreatment D-dimer level, μg/mL, median (IQR)	22.8 (11.9–34.2)

IQR, interquartile range; DWI, diffusion-weighted imaging.

Active cancer was defined as a diagnosis or treatment for any cancer within 6 months before stroke onset, or known recurrent cancer or metastatic disease. CAH-related stroke was defined using the following criteria: (1) pretreatment D-dimer value >3 μg/mL; (2) MVTIs; or (3) no other specific cause of stroke identified [6, 14]. We excluded patients who did not receive anticoagulant therapy or who did not have data on posttreatment D-dimer levels. The decision for antithrombotic therapy in individual patients was at the discretion of the treating physicians.

Measurements

We collected data about age, sex, vascular risk factors, use of antithrombotic agents, type of cancer, presence of metastases, cancer histology, cancer treatment, pre- and posttreatment D-dimer levels, vascular imaging, and DWI findings from medical records. Among D-dimer values measured >24 h from the initiation of anticoagulant therapy, the maximum value was used as the posttreatment D-dimer value. As an indicator of the trend in D-dimer levels by anticoagulant therapy, the ratio of posttreatment D-dimer level to pretreatment D-dimer level (post/pre ratio) was calculated and used for analysis.

Outcomes

Comprehensive medical records, including all in- and outpatient encounters, were reviewed from initial admission through December 31, 2021, to ascertain outcomes. The primary outcome was recurrent stroke while on anticoagulant therapy. Recurrent stroke was defined as a new lesion detected on DWI in patients with new acute neurological symptoms.

Statistical Analysis

Differences between pre- and posttreatment D-dimer levels in patients with and without recurrent stroke were analyzed with paired *t* tests. The post/pre ratio was compared between patients with and without recurrent stroke using the Wilcoxon rank-sum test. Fine-Gray models were used for the outcome of recurrent stroke, with death as the competing risk. In multivariate analysis, a forced-entry method was performed to identify whether the post/pre ratio was associated with recurrent stroke. Time-dependent receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic value of the post/pre ratio for predicting recurrent stroke, and area under the ROC curve was calculated. An optimal cutoff value was calculated using the Youden index. The level of significance was considered as 0.05 in all tests. All statistical analyses were performed using JMP version 14.2.0 (SAS Inc., Cary, NC, USA), SAS version 9.4 (SAS Inc., Cary, NC, USA), and R software version 4.1.1 (http://R-project.org) (The R Foundation for Statistical Computing, Vienna, Austria). The R library used was survival ROC (version 1.0.3).

Results

A flow diagram of patient selection is presented in Figure 1. The final cohort comprised 73 patients diagnosed with CAH-related stroke. Baseline characteristics are shown in Table 1. Anticoagulant therapy was initiated with continuous intravenous unfractionated heparin without bolus in 96% of patients because using low-molecular-weight heparin and novel oral anticoagulants for treatment of ischemic stroke is not covered by the Japanese health insurance. The mean duration of initial continuous intravenous unfractionated heparin was 13 days (SD: 6.5). The median follow-up time of all patients was 28 days (interquartile range [IQR] 11–65

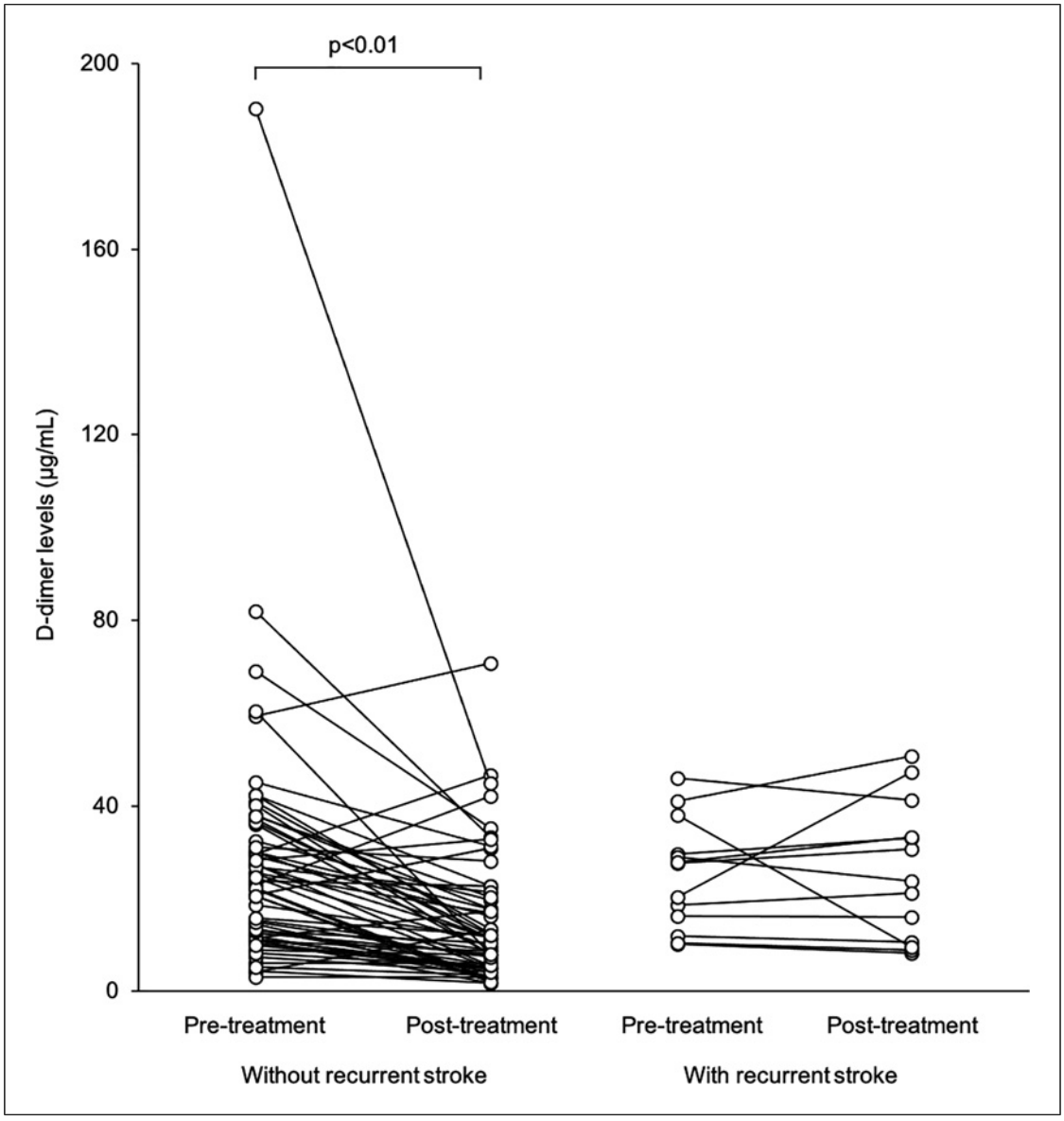

Fig. 2. D-dimer trends after anticoagulant therapy in patients with and without recurrent stroke.

days). During the observational period, oral anticoagulants were used in 23% of patients, comprising warfarin in 18%, edoxaban in 3%, apixaban in 1%, and dabigatran in 1%. Anticoagulant therapy was discontinued in 15 patients with end-stage cancer and 4 patients with active bleeding. The remaining 54 patients (74%) continued anticoagulant therapy until death or end of follow-up. Despite anticoagulant therapy, recurrent stroke occurred in 13 patients (18%). Among 13 patients with recurrent strokes, 12 (92%) had systemic metastases. The median number of posttreatment D-dimer measurements was 6 (IQR 4–9).

Figure 2 shows D-dimer trends after anticoagulant therapy in patients with and without recurrent stroke. The mean number of days for measuring posttreatment D-dimer value after initiation of anticoagulant therapy was 9 days (SD: 7.2). Patients without recurrent stroke displayed downward D-dimer trends after anticoagulant therapy (median 22.5 μg/mL [IQR 11.5–35.2 μg/mL] to 10.1 μg/mL [IQR 5.0–19.1 μg/mL], $p < 0.01$), whereas those with recurrent stroke showed neutral trends in high D-dimer levels after anticoagulant therapy (median 27.6 μg/mL [IQR 14.1–33.7 μg/mL] to 23.7 μg/mL [IQR 10.2–37.3 μg/mL], $p = 0.86$). Post/pre ratio was

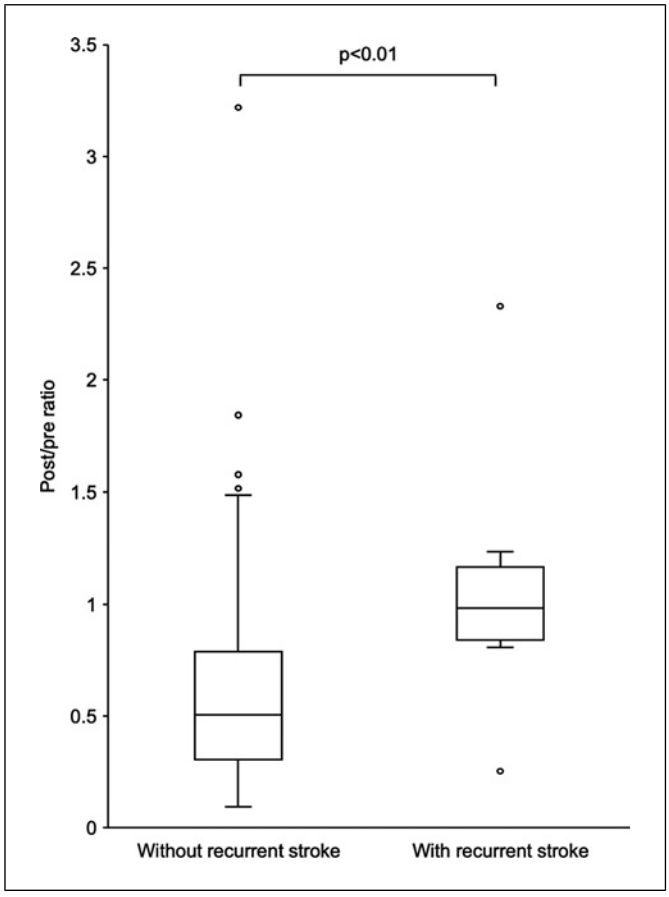

Fig. 3. Post/pre ratio in patients with and without recurrent stroke.

higher in patients with recurrent stroke than in those without (median 0.98 [IQR 0.85–1.17] vs. 0.51 [IQR 0.30–0.79], $p < 0.01$) (Fig. 3).

In univariate analysis, post/pre ratio and posttreatment D-dimer levels showed significant associations with recurrent stroke, whereas pretreatment D-dimer levels did not. Multivariate analysis revealed that high post/pre ratio was independently associated with recurrent stroke (per 0.1 increase, hazard ratio [HR] 2.20, 95% confidence interval 1.61–3.01; $p = 0.012$) (Table 2). In time-dependent ROC curve analyses, area under the curve for post/pre ratio was 0.813 at 30 days, and the optimal cutoff of 0.80 offered 92% sensitivity and 78% specificity.

Discussion

The results of this study showed that a neutral trend in high D-dimer levels even after anticoagulant therapy was associated with recurrent stroke in patients with CAH-related stroke. D-dimer levels decreased after anticoagulant therapy in most patients with CAH-related stroke. This result was similar to previous studies showing downward D-dimer trends after anticoagulant therapy in ischemic stroke patients with active cancer [15–18]. Downward D-dimer trends after anticoagulant therapy are also seen in patients with atrial fibrillation and deep venous thrombosis [21–23]. Anticoagulant therapy inhibits the activation of coagulation and fibrinolytic system, resulting in a decrease in D-dimer, a degradation product of thrombus [24]. Downward D-dimer trends after anticoagulation therapy seen in CAH-related stroke patients suggest successful suppression of hypercoagulability.

Patients with a neutral trend in high D-dimer levels even after anticoagulation therapy experienced a higher risk of recurrent stroke. In cancer patients with ischemic stroke, persistent high D-dimer levels after treatment and embolic signals were observed in 3 patients with early recurrent stroke [15]. Patients with persistently high D-dimer levels may have factors such as using inadequate anticoagulants, insufficient dosages of anticoagulants, or totally uncontrollable hypercoagulability. According to previous studies, cancer patients with recurrent strokes tended to have higher posttreatment D-dimer levels, but the difference was not significant [17, 18]. Since the present study focused on CAH-related stroke patients, D-dimer trends after treatment were enhanced, showing a significant difference between patients with and without recurrent stroke.

The optimal cutoff of the post/pre ratio for recurrent stroke was 0.8. Cancer patients often appear to be at high risk of bleeding due to local injury by tumor invasion or generalized hemorrhagic diathesis [25]. Even in such patients, instead of full-dose anticoagulants, a tentative therapeutic target of <80% of the initial D-dimer value might be preventive for short-term stroke recurrence. However, more appropriate therapeutic targets should be evaluated in prospective studies to assess both bleeding and ischemic risks.

We have to acknowledge several limitations in this study. First, the relatively small sample size and potential risk of selection bias owing to the two-center study. Second, recurrence might have been underdiagnosed due to the retrospective nature of data collection and the definition of stroke recurrence based on DWI findings. Third, comorbidities affecting D-dimer levels were not adequately assessed due to a lack of standardized testing. Some patients might have had comorbidities that affected changes in D-dimer values. Fourth, long-term prognosis

Table 2. Uni- and multivariate Fine-Gray models for recurrent stroke

	Univariate		Multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (per 1-year increase)	0.99 (0.94–1.04)	0.621	0.99 (0.97–1.02)	0.755
Sex, female	0.97 (0.33–2.82)	0.950	0.83 (0.47–1.48)	0.752
Hypertension	0.96 (0.30–3.10)	0.946	–	
Dyslipidemia	1.23 (0.33–4.61)	0.763	–	
Diabetes mellitus	1.63 (0.48–5.51)	0.433	–	
Current smoking	0.91 (0.18–4.58)	0.907	–	
Deep venous thrombosis	1.48 (0.50–4.35)	0.480	–	
Adenocarcinoma	1.11 (0.31–4.00)	0.870	–	
Systemic metastasis	1.96 (0.29–13.5)	0.493	–	
Recent chemotherapy	1.58 (0.54–4.64)	0.405	–	
DWI three territory sign	0.56 (0.18–1.79)	0.329	–	
Oral anticoagulant use	0.72 (0.20–2.62)	0.617	–	
Pretreatment D-dimer levels (per 1.0-μg/mL increase)	0.99 (0.98–1.01)	0.478	–	
Posttreatment D-dimer levels (per 1.0-μg/mL increase)	1.04 (1.01–1.06)	0.002	–	
Post/pre ratio (per 0.1 increase)	1.08 (1.01–1.15)	0.018	2.20 (1.61–3.01)	0.012

HR, hazard ratio; DWI, diffusion-weighted imaging.

could not be assessed due to early death and discontinuation of anticoagulant therapy with end-stage cancer. Fifth, the timing of measuring D-dimer values after treatment was heterogeneous. The optimal timing for measuring D-dimer values to determine treatment efficacy needs to be investigated in the future.

Conclusions

D-dimer levels after anticoagulant therapy were associated with recurrent stroke among CAH-related stroke patients. Patients showing a neutral trend in high D-dimer levels after anticoagulant therapy may appear to be at high risk of recurrent stroke.

Statement of Ethics

This study protocol was reviewed and approved by the Kyoto Prefectural University of Medicine Ethics Review Committee and the Institutional Review Board of Kyoto Second Red Cross Hospital in Kyoto, Japan, with approval number ERB-C-2064-1. The need to obtain informed consent for participation was waived because of the retrospective design and the minimal risk to patients.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

The study was conceived by Jun Fujinami, Yoshinari Nagakane, Tomoyuki Ohara, and Toshiki Mizuno. Jun Fujinami and Yoshinari Nagakane prepared the manuscript. Kei Fujikawa carried out the statistical analysis. Jun Fujinami, Shohei Murata, and Keiko Maezono contributed to data collection. All authors participated in the analysis and interpretation. The final version of the manuscript was reviewed and approved by all authors.

Data Availability Statement

Anonymized data not published within this article will be made available by request from any qualified investigator. Data are not publicly available due to ethical reasons. Further inquiries can be directed to the corresponding author.

References

1 Zöller B, Ji J, Sundquist J, Sundquist K. Risk of haemorrhagic and ischaemic stroke in patients with cancer: a nationwide follow-up study from Sweden. Eur J Cancer. 2012;48(12):1875–83.
2 Navi BB, Reiner AS, Kamel H, Iadecola C, Elkind MSV, Panageas KS, et al. Association between incident cancer and subsequent stroke. Ann Neurol. 2015;77(2):291–300.
3 Navi BB, Howard G, Howard VJ, Zhao H, Judd SE, Elkind MSV, et al. New diagnosis of cancer and the risk of subsequent cerebrovascular events. Neurology. 2018;90(23):e2025–33.
4 Jang H-S, Choi J, Shin J, Chung J-W, Bang OY, Kim G-M, et al. The long-term effect of cancer on incident stroke: a nationwide population-based cohort study in Korea. Front Neurol. 2019;10:52.
5 Dardiotis E, Aloizou A-M, Markoula S, Siokas V, Tsarouhas K, Tzanakakis G, et al. Cancer-associated stroke: pathophysiology, detection and management (Review). Int J Oncol. 2019;54(3):779–96.
6 Bang OY, Chung J-W, Lee MJ, Seo W-K, Kim G-M, Ahn M-J, et al. Cancer-related stroke: an emerging subtype of ischemic stroke with unique pathomechanisms. J Stroke. 2020;22(1):1–10.
7 Varki A. Trousseau's syndrome: multiple definitions and multiple mechanisms. Blood. 2007;110(6):1723–9.
8 Navi BB, Sherman CP, Genova R, Mathias R, Lansdale KN, LeMoss NM, et al. Mechanisms of ischemic stroke in patients with cancer: a prospective study. Ann Neurol. 2021;90(1):159–69.
9 Fujinami J, Ohara T, Kitani-Morii F, Tomii Y, Makita N, Yamada T, et al. Cancer-associated hypercoagulation increases the risk of early recurrent stroke in patients with active cancer. Cerebrovasc Dis. 2018;46(1–2):46–51.
10 Ohara T, Farhoudi M, Bang OY, Koga M, Demchuk AM. The emerging value of serum D-dimer measurement in the work-up and management of ischemic stroke. Int J Stroke. 2020;15(2):122–31.
11 Gon Y, Okazaki S, Terasaki Y, Sasaki T, Yoshimine T, Sakaguchi M, et al. Characteristics of cryptogenic stroke in cancer patients. Ann Clin Transl Neurol. 2016;3(4):280–7.
12 Finelli PF, Nouh A. Three-territory DWI acute infarcts: diagnostic value in cancer-associated hypercoagulation stroke (trousseau syndrome). AJNR Am J Neuroradiol. 2016;37(11):2033–6.
13 Shen Y, Li Y, Chen C, Wang W, Li T. D-dimer and diffusion-weighted imaging pattern as two diagnostic indicators for cancer-related stroke: a case-control study based on the STROBE guidelines. Medicine. 2020;99(4):e18779.
14 Maezono-Kandori K, Ohara T, Fujinami J, Makita N, Tanaka E, Mizuno T. Elevated CA125 is related to stroke due to cancer-associated hypercoagulation. J Stroke Cerebrovasc Dis. 2021;30(12):106126.
15 Seok JM, Kim SG, Kim JW, Chung C-S, Kim G-M, Lee KH, et al. Coagulopathy and embolic signal in cancer patients with ischemic stroke. Ann Neurol. 2010;68(2):213–9.
16 Lee MJ, Chung J-W, Ahn M-J, Kim S, Seok JM, Jang HM, et al. Hypercoagulability and mortality of patients with stroke and active cancer: the OASIS-CANCER study. J Stroke. 2017;19(1):77–87.
17 Jang H, Lee JJ, Lee MJ, Ryoo S, Yoon CH, Kim G-M, et al. Comparison of enoxaparin and warfarin for secondary prevention of cancer-associated stroke. J Oncol. 2015;2015:502089.
18 Nakajima S, Kawano H, Yamashiro K, Tanaka R, Kameda T, Kurita N, et al. Post-treatment plasma D-dimer levels are associated with short-term outcomes in patients with cancer-associated stroke. Front Neurol. 2022;13:868137.
19 Ito S, Kikuchi K, Ueda A, Nagao R, Maeda T, Murate K, et al. Changes in serial D-dimer levels predict the prognoses of trousseau's syndrome patients. Front Neurol. 2018;9:528.
20 Nam K-W, Kim CK, Kim TJ, An SJ, Oh K, Mo H, et al. Predictors of 30-day mortality and the risk of recurrent systemic thromboembolism in cancer patients suffering acute ischemic stroke. PLoS One. 2017;12(3):e0172793.
21 Lip GY, Lowe GD, Rumley A, Dunn FG. Increased markers of thrombogenesis in chronic atrial fibrillation: effects of warfarin treatment. Heart. 1995;73(6):527–33.
22 Siegbahn A, Oldgren J, Andersson U, Ezekowitz MD, Reilly PA, Connolly SJ, et al. D-dimer and factor VIIa in atrial fibrillation: prognostic values for cardiovascular events and effects of anticoagulation therapy. A RELY substudy. Thromb Haemost. 2016;115(5):921–30.
23 Couturaud F, Kearon C, Bates SM, Ginsberg JS. Decrease in sensitivity of D-dimer for acute venous thromboembolism after starting anticoagulant therapy. Blood Coagul Fibrinolysis. 2002;13(3):241–6.
24 Zhang L, Long Y, Xiao H, Yang J, Toulon P, Zhang Z. Use of D-dimer in oral anticoagulation therapy. Int J Lab Hematol. 2018;40(5):503–7.
25 Kamphuisen PW, Beyer-Westendorf J. Bleeding complications during anticoagulant treatment in patients with cancer. Thromb Res. 2014;133(Suppl 2):S49–55.